Review Article

Vaccination versus natural infection: A review of antibody differentiation techniques

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The production of specific antibodies occurs in response to pathogens, whether encountered naturally or introduced through vaccination, serving as markers of immunity. As novel vaccines are developed and deployed, especially in response to emerging infectious diseases, the ability to distinguish between vaccine-induced and infection-induced antibodies becomes increasingly important. Vaccines are designed to mimic this natural infection process without causing the disease itself. Serological assays are critical tools in immunology, enabling researchers and clinicians to differentiate between antibodies produced by vaccination and those generated by natural infection. By understanding whether an individual's antibodies are the result of previous infection or vaccination, healthcare providers can modify booster recommendations more effectively. It also plays an important role in identifying people with hybrid immunity and in assessing the effectiveness of vaccination campaigns.

Key words: Antibody differentiation, hybrid immunity, natural infection, serological assays, vaccine-induced immunity

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INTRODUCTION

In immunology, the differentiation between antibodies produced by vaccination and those generated by natural infection has become a critical area of study, particularly with the global focus on vaccination strategies during health crises such as the COVID-19 pandemic.[1] The immune system's response to pathogens, whether encountered naturally or introduced through vaccination, involves the production of specific antibodies that serve as markers of immunity. Understanding the modulation of these immune responses is essential for assessing individual immune status, evaluating vaccine efficacy, and guiding public health interventions.[2]

As novel vaccines are developed and deployed, especially in response to emerging infectious diseases, the ability to distinguish between vaccine-induced and infection-induced antibodies becomes increasingly important. For example, during the COVID-19 pandemic, more than 12 billion vaccine doses were administered globally by the end of 2023, contributing to a significant increase in the population's immune coverage.[3] However, studies have shown that up to 40% of individuals may harbor antibodies due to natural infection, which complicates the assessment of vaccine-induced immunity.[4] This distinction is crucial for understanding the long-term protection offered by vaccines and identifying individuals who have experienced natural infection, which may provide broader immunity. Furthermore, this knowledge is vital to monitoring population-level immunity and making informed decisions about booster vaccinations, hybrid immunity, and the need for continued serological surveillance.[5]

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By exploring the mechanisms of antibody production, specific antigenic targets, and the role of serological assays, this review highlights the clinical and public health implications of these findings, ultimately contributing to more effective vaccination strategies and better management of infectious diseases.

METHODS

Search strategy

Inclusion criteria

Inclusion criteria were (i) studies that focus on the objective of this article, (ii) studies published in the past decade, (iii) studies that match the objective of this study, and (iv) studies written in the English language.

Exclusion criteria

Exclusion criteria were (i) Studies written as editorials, book chapters, case series, short communication, or letter to editor; (ii) studies unavailable in full-text; (iii) studies published are not in the English language, and (iv) studies whose findings were considered does not match the objective of the study.

Data extraction

Google Scholar and PubMed search engines were used, and MeSH terms were "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] AND "infectants"[All Fields] OR "infected"[All Fields] OR "infected"[All Fields] OR "infectibility"[All Fields] AND "immune"[All Fields] OR "immuned"[All Fields] OR "immunes"[All Fields] OR "immunization"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "immunization"[All Fields] AND "immunologie"[All Fields] OR "immunology"[Subheading] OR "immunology"[All Fields] AND "memory b cells"[MeSH Terms] OR "memory b cells"[All Fields] OR "memory b cell"[All Fields] AND "antigen's"[All Fields] OR "antigene"[All Fields] OR "antigens"[All Fields] OR "antigenic"[All Fields] OR "antigenically"[All Fields] OR "antigenicities"[All Fields] [Figure 1].

MECHANISMS OF ANTIBODY PRODUCTION

Antibody production is a fundamental aspect of the immune system's response to foreign invaders, whether these invaders are naturally occurring pathogens or antigens introduced through vaccination. This complex process begins with activating B cells, a type of white blood cell that plays a crucial role in adaptive immunity.[6] When the immune system encounters an antigen, whether it is a virus, bacterium, or a vaccine component, it recognizes specific molecular structures on the antigen's surface. These structures are known as epitopes and their recognition is key to initiating the immune response [Figure 2].[7]

Once B cells recognize these epitopes through their surface receptors, they undergo a process known as clonal expansion, where they multiply and differentiate into two main types of cells: plasma cells and memory B cells.[8] Plasma cells are the antibody-secreting factories of the immune system. Each plasma cell produces antibodies that are specific to the antigen that triggered the immune response. These antibodies then circulate in the bloodstream, binding to the antigen, neutralizing it, or marking it for destruction by other immune cells [Figure 2].[6]

Vaccines are designed to mimic this natural infection process without causing the disease itself. They achieve this by presenting the immune system with harmless forms of the pathogen, such as inactivated or attenuated viruses, protein subunits, or viral proteins.[9] For example, mRNA vaccines, such as those used against COVID-19, provide cells with the genetic instructions to produce a piece of the virus, typically the spike protein. The immune system then recognizes this protein as foreign, initiating an immune response that includes the production of specific antibodies [Figure 3].[10]

The artificial introduction of antigens through vaccination stimulates the immune system in a controlled manner, allowing it to develop a memory of the pathogen without the risk of disease.[11] Memory B cells, generated during natural infection and vaccination, remain in the body long-term, ready to respond more rapidly and effectively if the same pathogen is encountered again. This ability to "remember" the pathogen underlies the concept of immunity, which is the cornerstone of vaccine efficacy [Figure 3].[12]

ANTIGENIC TARGETS

The distinction between vaccine-induced and infection-induced antibodies is largely based on the specific antigenic targets that the immune system recognizes and responds to. These antigenic targets are the parts of the pathogen that the immune system recognizes, triggering the production of antibodies. Understanding these goals is crucial for differentiating between immunity that arises from vaccination and that results from natural infection.[13]

In the COVID-19 situation, this distinction is particularly evident. COVID-19 vaccines, such as those developed by Pfizer-BioNTech and Moderna, are designed to target the spike protein of the SARS-CoV-2 specifically.[14] The spike protein is the key structure that the virus uses to enter human cells, and it is also the primary target for neutralizing antibodies that block infection. When a person is vaccinated, their immune system is trained to recognize this spike protein,

leading to the production of antibodies that can prevent the virus from infecting cells if they are later exposed.[15]

Natural infection with SARS-CoV-2 exposes the immune system to the entire virus, not just the spike protein. As a result, individuals who have been infected with the virus naturally develop antibodies against multiple components of the virus, including the nucleocapsid protein, which is a structural protein inside the virus. The presence of antinucleocapsid antibodies is a clear marker of past infection because these antibodies are not produced in response to spike protein-only vaccines.[15]

This difference in antigenic targets is critical for serological tests and epidemiological studies. For example, the detection of antinucleocapsid antibodies in a person's blood can confirm that they have previously been infected with SARS-CoV-2, while the presence of antispike antibodies alone could indicate either vaccination or natural infection.[16] Understanding these differences allows clinicians and public health officials to more accurately assess an individual's immune status, the extent of vaccine coverage in a population, and the prevalence of past infections, contributing to more informed public health decisions and vaccine strategies.[17]

SEROLOGICAL ASSAYS AND BIOMARKERS

Serological assays are important tools in immunology. They allow researchers and clinicians to differentiate between antibodies produced by vaccination and those generated through natural infection. These assays are designed to detect and measure specific antibodies in the blood, providing information on an individual's immune status and helping to determine whether immunity was acquired through vaccination or as a result of natural infection.[18]

One key way serological assays achieve this distinction is by targeting specific antibodies associated with different parts of a pathogen. For example, in the case of SARS-CoV-2, serological assays can be designed to detect antibodies against spike protein, typically induced by vaccines, or against the nucleocapsid protein, which is associated with natural infection.[19] By measuring the presence and levels of these antibodies, clinicians can discern whether an individual has been vaccinated, has had a past infection, or possibly both.[20]

Advanced serological techniques improve the accuracy and reliability of these assessments. The enzyme-linked immunosorbent assay (ELISA) is one of the most widely used methods, capable of detecting and quantifying specific antibodies with high sensitivity.[21] ELISA works using antigens immobilized on a surface to capture antibodies from a blood sample. This is followed by a detection process that signals the presence of targeted antibodies.[22]

Neutralization assays are another powerful tool, particularly for assessing the functional ability of antibodies to prevent viral entry into cells. These assays measure the effectiveness of antibodies in blocking infection, providing not only qualitative data on the presence of antibodies but also quantitative information on their protective potential.[23]

Multiplex serology represents a more advanced approach, allowing the simultaneous detection of multiple types against different antigens in a single assay. This technique provides a comprehensive antibody profile, making it easier to distinguish between vaccine-induced and infection-induced antibodies and offering a broader understanding of an individual's immune response.[24]

In general, these serological assays and biomarkers are indispensable for accurately differentiating antibody sources, helping to evaluate vaccine efficacy, detecting past infections, and developing public health strategies [Table 1].

ROLE OF MEMORY B-CELLS AND LONG-TERM IMMUNITY

Memory B-cells play a crucial role in the immune system's ability to provide long-term protection against pathogens, whether the immune response is triggered by vaccination or natural infection.[25] These cells are a key component of the adaptive immune system. They "remember" the specific antigens that they have encountered, allowing for a faster and more robust response if the same pathogen is reencountered.[26]

During vaccination and natural infection, B-cells are activated and differentiate into plasma cells, which produce antibodies, and memory B-cells, which persist long after the initial exposure. These memory B-cells remain in the body for years, sometimes even decades, ready to rapidly produce antibodies upon reexposure to the antigen. This mechanism underlies the concept of immunity, as it provides long-term protection against diseases.[27]

However, the durability and specificity of memory B-cell responses can vary depending on whether antigen exposure comes from a vaccine or a natural infection. Natural infection often involves exposure to a larger array of viral or bacterial antigens, leading to the production of a more diverse set of memory B-cells.[25] This broader immune response can provide more robust and durable protection, especially in the context of heterologous immunity, where the immune system recognizes and responds to different but related pathogens.[28]

Table 1: Comparison of serological assays for antibody differentiation[21-24]

Assay type	Target antigens	Sensitivity	Specificity	Key advantages	Limitations
ELISA	Spike, nucleocapsid	High	High	Quantitative, widely available	Limited to antigen detection
Neutralization assay	Spike protein	Moderate	High	Measures functional antibodies	Labor-intensive, costly
Multiplex serology	Spike, nucleocapsid	High	High	Detects multiple antigens at once	Requires specialized equipment
Rapid lateral flow assay	Spike protein	Moderate	Moderate	Point-of-care use, fast results	Lower sensitivity than ELISA

ELISA=Enzyme-linked immunosorbent assay

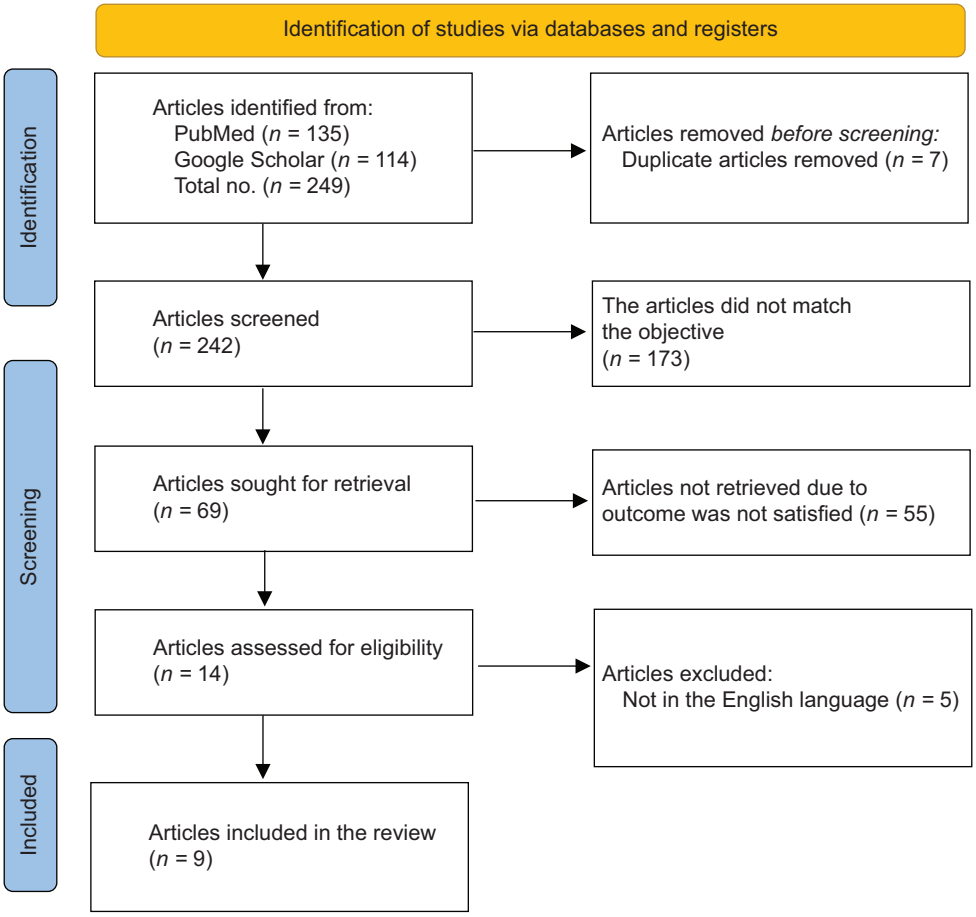

Figure 1: PRISMA

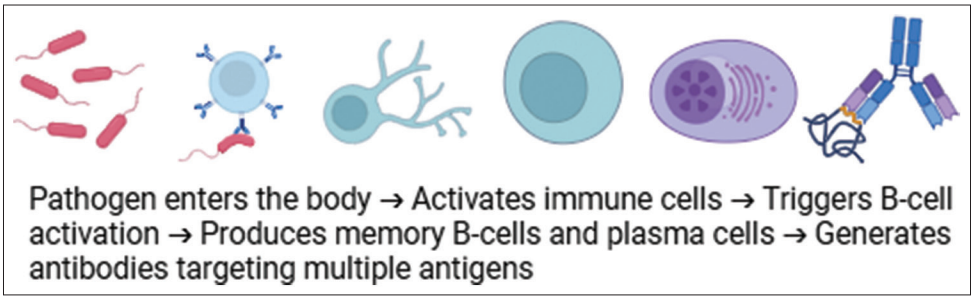

Figure 2: Natural infection[6-8]

Vaccines generally target specific antigens, such as the SARS-CoV-2 spike protein in COVID-19 vaccines. Although this targeted approach is highly effective in preventing disease, the resulting memory B-cell memory response can be narrower in scope compared to natural infection.[29] This can sometimes result in a less durable or less broad immune memory, particularly when it comes to variants of the pathogen that differ significantly from the target vaccine.

The polio vaccines typically target specific antigens, such as the Inactivated poliovirus vaccine (IPV) or attenuated live poliovirus vaccine (OPV), to induce immunity.

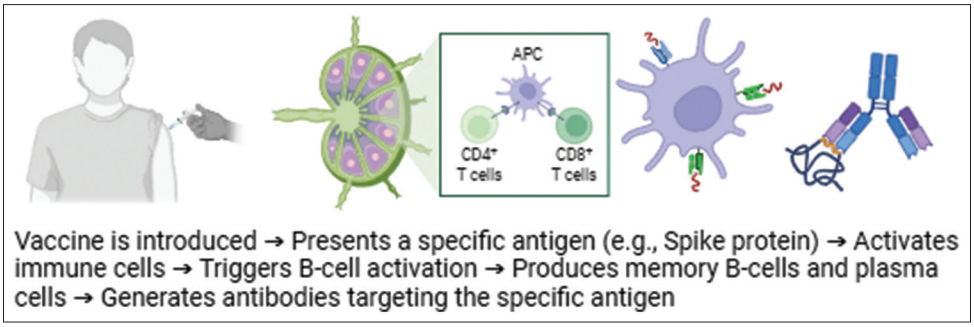

Figure 3: Vaccine-induced infection[9-12]

This targeted approach is highly effective in preventing poliomyelitis, but the memory B-cell response that results from this may be narrower in scope than that from natural infection.[30] T-cell help and germinal center reactions are important for affinity maturation and long-term B-cell memory and influence the quality and durability of this response.[31] Strong T-cell help is still associated with primarily systemic IPV, while mucosal stimulation to generate strong intestinal immunity is lacking. OPV elicits mucosal immunity but results in waning protection with time, thus impairing the breadth of immune memory and its control of viral transmission.[32]

Studies have shown that individuals who have recovered from natural infections can develop a more comprehensive and long-lasting immune memory compared to those who have only been vaccinated.[7,33,34] This is particularly evident in the context of heterologous immunity, where the B-cells generated by natural infection can provide cross-protection against different strains or related pathogens. Understanding these differences is critical to designing effective vaccination strategies and anticipating the longevity and breadth of immunity in populations.[35]

CLINICAL IMPLICATIONS AND PUBLIC HEALTH CONSIDERATIONS

The accurate differentiation between antibodies produced by vaccination and those generated by natural infection carries profound clinical and public health implications. This distinction is essential to inform various aspects of healthcare and disease management, particularly in the context of widespread vaccination campaigns and ongoing infectious disease surveillance.[36]

One of the primary clinical applications is in the decision-making process for booster vaccinations. By understanding whether an individual's antibodies are the result of prior infection or vaccination, healthcare providers can tailor booster recommendations more effectively.[37] For example, people who have both vaccine-induced and infection-induced antibodies referred to as having hybrid immunity may exhibit stronger and more durable immune responses. Recognizing this could influence the timing and necessity of booster doses, potentially optimizing immunity in the population and reducing the frequency of booster administrations.[38]

Furthermore, distinguishing between these antibody sources is crucial to identifying individuals with hybrid immunity. Hybrid immunity, which results from a combination of vaccination and natural infection, has been shown to provide better protection against reinfection, including against variants of concern.[39] Monitoring the prevalence of hybrid immunity within a population can help public health officials assess general community immunity levels and predict the potential impact of future outbreaks.[40]

From a public health perspective, these distinctions are vital for accurate serological surveillance and the monitoring of population-level immunity. Knowing whether antibodies in a population are predominantly from vaccination or natural infection helps assess the effectiveness of vaccination campaigns and understand the spread of the virus.[41] This information is especially important in evaluating the success of public health strategies and in making informed decisions about resource allocation, such as where to prioritize vaccination efforts or when to implement additional public health measures.[42]

Furthermore, distinguishing between vaccine-induced and infection-induced antibodies is critical for assessing vaccine breakthrough cases, in which individuals contract the disease despite being fully vaccinated. Understanding the prevalence and characteristics of these cases can provide information on vaccine efficacy, the impact of emerging variants, and the need for potential updates to vaccine formulations.[43]

Ultimately, the ability to differentiate between these sources of antibodies improves our understanding of immunity dynamics, informs clinical practice, and strengthens public health responses, all of which are essential for managing current and future challenges of infectious disease challenges.[44]

CHALLENGES AND LIMITATIONS

Serological tests are indispensable in discriminating between the presence of vaccine-induced versus infection-induced antibodies; however, they also possess various limitations and challenges. ELISA provides great sensitivity but does not assess functionality; on the other hand, the neutralization assay is more biologically relevant, although it is more cumbersome and expensive with specialized laboratory setups.[45] Cross-reactivity also occurs when the antibody has previously interacted with similar infections, and will also lead to false positives. In addition, universally accepted standards lack in comparing results of serological assays between studies and laboratories due to variability in the selection of antigens, methods for detection, and interpretation.[46]

Further complicating matters is temporal variation in antibody levels due to the phenomenon of antibody waning with time, thereby confounding assay accuracy in differentiating between a recent infection and a long-term immune response. Many assays primarily target spike or nucleocapsid proteins, potentially missing other immunological markers that could enhance differentiation, although emerging technologies such as multiplex serology and machine-learning-based approaches may help address this limitation.[47] Variability in individual immune responses further complicates serological testing, as host factors such as age, genetics, comorbidities, and prior pathogen exposure influence antibody production, with elderly and immunocompromised individuals often showing diminished responses. Hybrid immunity, caused by infection and vaccination, leads to broader and stronger immune responses, making it harder to differentiate natural from vaccine-induced immunity.[48]

Heterologous immunity, where prior exposure to related pathogens alters immune responses unpredictably, can also interfere with serological tests. The lack of universally recognized reference materials results in variability in the calibration of assays and differences in laboratory protocols, reagents, and equipment to yield inconsistent results and highlight the need for an international standardized framework.[28] Even in standardized assays, the task of estimating protective immunity remains very complex, as a relationship between antibody presence and protection is not always evident given the predominant role of T-cell immunity. Another reason is that advanced serological assays, such as neutralization and multiplex assays, are expensive and require technical expertise, thus not easily accessible in low-resource settings.[19] These issues will be solved by continuous research, better designs of assays, and the development of universally accepted guidelines for antibody differentiation. A combination of serological testing, functional assays, and cellular immunity assessments may provide a more comprehensive understanding of immune protection following infection or vaccination.[49]

To overcome the limitations of current serological methods, new assays and biomarkers are emerging to improve accuracy. Next-generation assays with high-throughput screening, biosensors, and microfluidic platforms enhance the sensitivity and specificity of the serological tests.[50] AI-driven data analysis helps identify patterns of antibodies that distinguish natural from vaccine-induced immunity. The emerging biomarkers include T-cell activation markers and cytokine signatures, which provide a more comprehensive immune assessment.[51] Multiplex and multiomics approaches that integrate proteomics, genomics, and metabolomics for refined immune profiling to support personalized vaccination strategies are necessary to advance these technologies to improve antibody differentiation and global public health preparedness.[52]

CONCLUSION

Differentiating between vaccine-induced and infection-induced antibodies is a complex, yet essential, task in immunology. Advances in serological assays and a deeper understanding of immune responses to various antigens have significantly improved our ability to make these distinctions. This knowledge is important for guiding clinical decisions, such as determining the need for booster vaccinations, and for understanding population-level immunity. It also plays a crucial role in identifying individuals with hybrid immunity and in assessing the effectiveness of vaccination campaigns. Continued research in this area will further enhance our ability to interpret serological data accurately, ultimately contributing to more effective public health strategies and better management of infectious diseases.

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Conflicts of interest

There are no conflicts of interest.

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